Hair : Therapy & Transplantation

Letter to the Editor **Open Access**

Lichen Planopilaris-histologic Criteria & Clues in Vertical Sections

Michael Wilk[1]*, Bettina G Zelger[2] and Bernhard Zelger[3]

[1]Dermatohistological Laboratory and Private Practice, Nuernberg, Germany
[2]Institute of Pathology, Medical University Innsbruck, Austria
[3]Clinical Department of Dermatology & Venerology, Medical University Innsbruck, Austria

Abstract

We report on our histological experience in 47 patients with lichen planopilaris/frontal fibrosing alopecia. Besides presenting the spectrum of clinical appearance of the disease we emphasize the importance of vertical histologic sections of biopsies in the clinicopathological work-up of these patients and give precise histologic criteria and clues in different stages of the disease. Immunohistologically, we found a marked reduction of epithelial Ki-67 expression next to the inflammatory process especially evident in advanced stages of disease.

Keywords: Lichen planopilaris; Frontal fibrosing alopecia; Dermatopathology

To the Editor

Lichen planopilaris (LPP) is considered to represent a variant of lichen planus which predominantly affects the scalp. In LPP cutaneous lesions elsewhere on the body except the scalp have been reported in up to 50% of cases [1-4], before, concurrent as well as after the onset of LPP [1]. Mucous membranes, nails as well as hair-bearing and non-hair-bearing areas of the body have been reported to be involved, and this may sometimes be helpful when the diagnosis of LPP is in doubt or difficult from a clinical and/or dermatohistopathological point of view. Clinically, LPP presents as a multifocal, reticulated area of hairloss with perifollicular erythema sometimes accompanied by scales. Individual hairs may be preserved. In time the disease leads to follicular hyperkeratosis, follicular fusion, whitish scarring with loss of follicular orifices and mottled hyperpigmentation. The disease may also present as frontal fibrosing alopecia (FFA) [5-10] and Graham-Little-syndrome when eyebrows, axillae and/or pubic hair are involved as well combined with widespread keratotic papules on the trunk and extremities (Figure 1). While the simultaneous occurrence of LPP and FFA has been reported in up to 14% of patients [6], scalp involvement in the latter tends to be localized and not multifocal, occurs mostly in postmenopausal women and is only rarely associated with lesions of lichen planus [5-10]. However, eyebrow and especially upper limb alopecia with scarring appear to be more common in FFA than previously reported [10]. Thus, lichen planus, LPP and FFA appear to represent a spectrum of disease with clinical overlap and similar histological features. Both, LPP and FFA tend to scarring alopecia which makes the accurate diagnosis an urgent and important matter.

In contrast to lichen planus, LPP and FFA are much more commonly reported in women [1-4,8,11,12]. This is similar to lupus erythematosus and other autoimmune disorders which are more commonly seen in (young) women. Alternatively or complementary to the above, this may be an underestimate of the true prevalence in men due to the fact that women to some degree more frequently seek medical advice because of hair loss and the simultaneous occurrence of common baldness in men, possibly in part patients with fibrosing alopecia in male pattern distribution. The difference in gender is also reflected by our study of 39 women and 8 men diagnosed to suffer from LPP/FFA at the out-patient clinic/histological laboratory of the Department of Dermatology University of Innsbruck (n=37) or sent as histologic consultation cases (n=10) between 2006 and 2013. The average age of men and women at presentation was also different with 55 (range 27-78) and 42 (range 23-67) years, respectively.

Despite advances in diagnostic procedures using microarray

analysis and new insights into possible pathogenetic factors in primary cicatricial alopecia (such as loss of immune protection of stem cells, lipid metabolism dysregulation, impaired self-maintenance of hair

Figure 1: The clinical appearance of LPP.
A. Fully developed LPP. Patchy, multifocal, reticulated loss of hair with residual single hairs and tufts of hairs.
B. Fully developed LPP (FFA). Patchy, multifocal loss of hair at the right temple accompanied by mottled pigmentation and initial scarring. Single hairs are preserved.
C. Late LPP (FFA). There is fronto-lateral diffuse loss of hair accompanied by mottled hyperpigmentation and whitish scarring. Note also alopecia of eyebrows.
D. Late LPP. There is an area of patchy, confluent loss of hair, individual hairs are preserved. Perifollicular, mottled pigmentation and hypopigmentation due to scarring are evident.
E. Follicular LPP. There are disseminated follicular red-brownish papules on the trunk.

*Corresponding author: Michael Wilk, Dermatohistological Laboratory and Private Practice, Postfach 4145, 90021 Nuernberg, Germany, Tel: +49 911 223690; Fax: +49 911 209816; E-mail: M.Wilk@t-online.de

follicle stem cells, increased apoptosis, enhanced autoimmunity by pro-inflammatory cytokines and environmental/genetic predisposition, neurogenic skin inflammation) the precise mechanisms that provoke the destructive reaction to the hair follicle, including LPP and FFA, remain to be elucidated [13,14]. Thus, at present primary cicatricial alopecias are best classified according to their clinical presentation and histopathological pattern.

While the clinical presentation of scarring alopecia may sometimes be non-specific and misleading, in our experience the vertical histological examination of biopsies taken from active lesions allows a precise diagnosis in the vast majority of cases (Figure 2). Diagnosis follows a stepwise approach from scanning to medium- and high power magnifications. On one hand vertical in contrast to horizontal technique allows to recognize on scanning magnification dermatologic disorders which mainly affect the interfollicular epidermis. These occur more commonly on non-hairy skin, but just by chance are seen in hairy areas, too or exclusively, such as eczema or psoriasis, to mention the most classic dermatoses. Furthermore, LPP/FFA is a superficial lichenoid disease and as such is best differentiated from lupus erythematosus and lichen sclerosus et atrophicus when the interfollicular epidermis is available for study. On the other hand identifying the level of disease with scanning magnification is especially helpful to evaluate deeper located inflammatory diseases such as alopecia areata. So, in a vertical section not only a "swarm of bees" around follicular papillae is diagnostic of active/full-blown stage of alopecia areata, but also a foreign-body granuloma to released hair-shaft material in circumscribed subcutaneous location which may obscure and complicate early peracute lymphocytic peribulbitis or some rare late stage of alopecia areata.

At intermediate magnification vertical sectioning allows to investigate epithelial (spongiosis, acantholysis, ballooning, interface) and stromal changes (granulation tissue, granulomas, scarring, mucin, fibrosis, sclerosis). The presence of prominent dermal mucin in lupus erythematosus and the location of subepidermal reduction of elastic fibers in lichen sclerosus et atrophicus are further helpful criteria for differential diagnosis.

Finally, at high power magnification the type of inflammatory cell involved should be investigated (lymphocytes, macrophages, neutrophils, plasma cells, fibrocytes, dendritic cells) in case supplemented by special stains for fungi, spirochetes, other bacteria and herpes virus to rule out infectious disease processes. Direct immunofluorescence and additional laboratory tests (KOH examination for fungi, cultures, ANA, TPHA, etc.) may be helpful to come to a definite diagnosis [1,2,11,15-17].

Studying vertical sections in LPP/FFA one has to be aware that not all criteria listed below are met in one slide. Therefore at times the method of horizontal sections may be a valid complement, especially in non-scarring variants of alopecia [17-20]. They enable the histopathologist to investigate more follicles, which may be in different stages of disease, in one plane. However, good laboratory handling & practice as well as medical experience with these techniques are essential. Therefore, in our opinion, when only one biopsy in - clinically scarring - alopecia is available and LPP versus lupus erythematosus is the differential diagnosis, a vertical work-up of the biopsy should be performed.

Reviewing 47 biopsies of LPP/FFA, we found the following criteria and clues in vertical sectioning especially helpful for an accurate diagnosis of this disease, many of them confirming findings of previous studies [1,2,4,7,8,11,12,15-17,21,22]. Notably, most of our specimens represent advanced stages of disease stressing the need to establish the correct diagnosis as early as possible.

Early (n=5; all females)

Signs similar to classic lichen planus, such as lichenoid peri-infundibular lymphocytic inflammation ("hugging type" [22]), reactive epidermal and infundibular hyperplasia (Figure 2A). The inflammatory infiltrate can sometimes involve the deep reticular dermis and thus simulate other more deeply located dermatoses especially lupus erythematosus. Further signs are basal cell vacuolization, necrotic keratocytes or apoptoses (so-called cytoid or Civatte bodies), wedge-shaped hypergranulosis and superficial pigment incontinence.
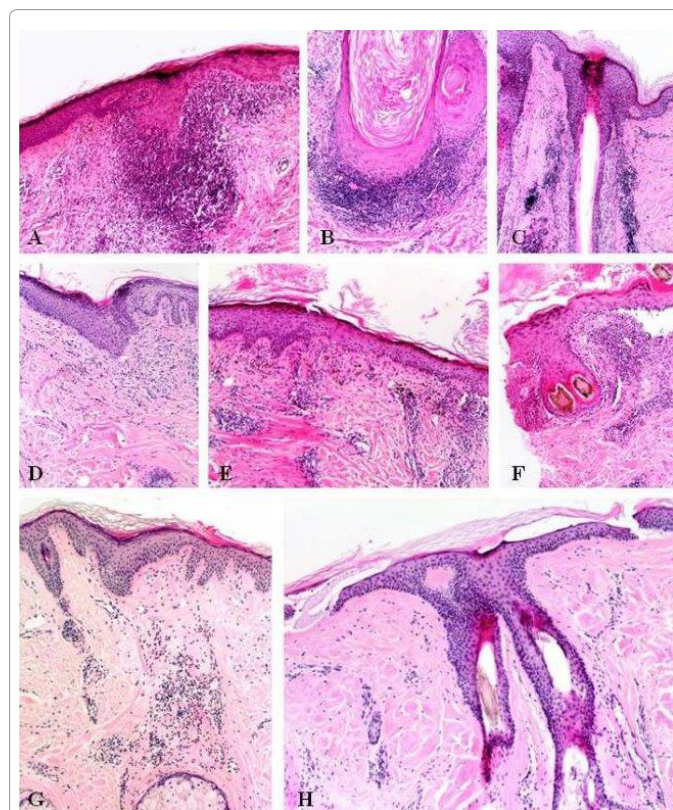

Figure 2: Histology of LPP in different stages of the disease (H&E).
A. Early LPP. There is infundibular hyperplasia, wedge-shaped hypergranulosis and a dense perifollicular ("hugging type") lichenoid infiltrate composed mainly of lymphocytes with little pigment incontinence and mild fibrosis.
B. Fully developed LPP. Infundibular hyperplasia and follicular plugging accompanied by a dense lichenoid infiltrate of lymphocytes, pigment incontinence and necrotic keratocytes/apoptosis ("cytoid or Civatte bodies").
C. Fully developed LPP. Periinfundibular fibrosis and residual inflammation that "backs away" from the follicle.
D. Late LPP. Infundibular hyperplasia with wedge-shaped, superficial perifollicular fibrosis and alopecia.
E. Late LPP. There is a residual lymphocytic inflammatory infiltrate with pigment incontinence, dilated capillaries (indicator of - previous - inflammatory process) and fibrosis in the superficial dermis.
F. Late LPP. Infundibular hyperplasia with compact orthohyperkeratosis, hypergranulosis and infundibular tufts (compound follicles) accompanied by superficial scarring, subepidermal clefts and a lymphocytic inflammatory infiltrate.
G. Late LPP. Beneath an unremarkable epidermis there is superficial fibrosis with residual lymphocytic inflammation and teleangiectasia.
H. Late LPP. Infundibular tufts (compound follicles) are evident. Note that the fusion occurs at the level of the infundibulum. There is mild perifollicular fibrosis.
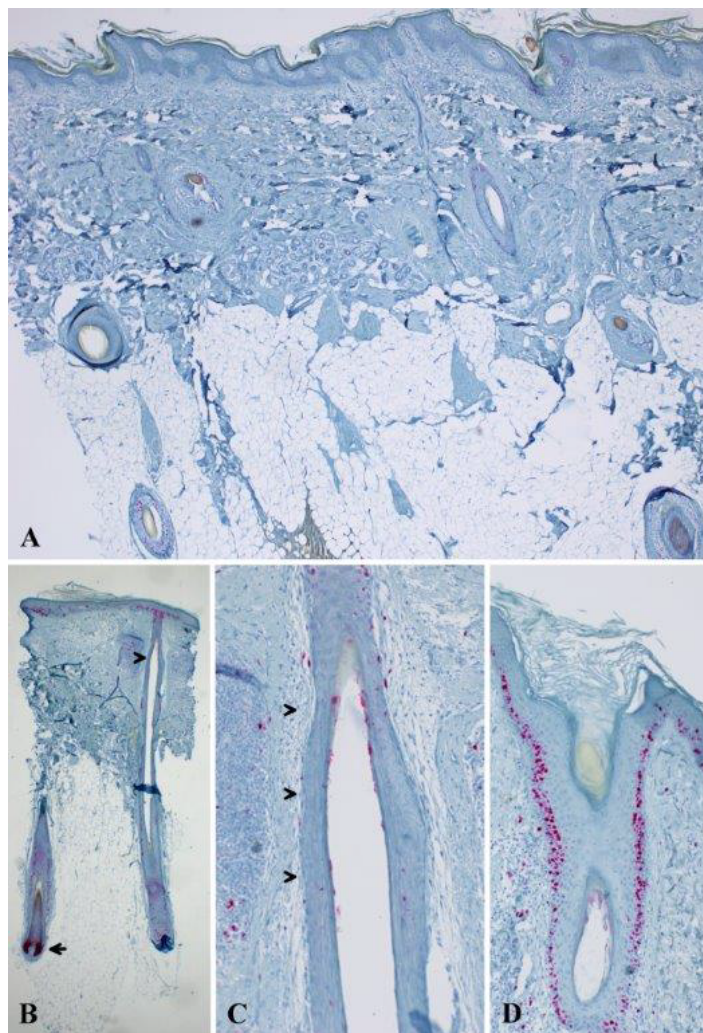
Figure 3: Ki-67 immunohistology of LPP.
A. Late LPP. Diminished hair density and a marked reduction of Ki-67 expression of involved hair follicles and the overlying epidermis.
B., C. Fully developed LPP. Next to the hair bulge there is lymphocytic inflammation and fibrosis. Note the marked reduction of Ki-67 expression of follicular epithelium in this area (arrowheads). The bulb shows a normal Ki-67 immunostaining and therefore appears not to be involved in the disease process (arrow).
D. For comparison: Ki-67 immunohistology of the upper part of a hair follicle next to a melanocytic nevus in otherwise normal skin.

Fully developed (n=30; 23 females, 7 males)

Follicular plugging, presence of a superficial perivascular lymphocytic inflammation with pigment incontinence, clefts between epithelium and dermis. Loss of sebaceous glands and stem cells (in case verified with anti-CK15 [23,24]), initial fibrosis (Figure 2B and 2C).

Late (n=11; 10 females, 1 male)

Thinning of follicular epithelium, peri-infundibular, superficial scar embracing the infundibulum accompanied by perifollicular mucin and wedge-shaped loss of elastic tissue, scant lymphocytic inflammation that "backs away" [16] from the follicle, infundibular tufts/follicular fusion (compound follicles) due to mild scarring around hair follicles and their infundibula in particular (which is in contrast to tufted folliculitis or folliculitis decalvans where a much more destructive and granulomatous scarring reaction accompanied by neutrophils is seen). Marked reduction of hairs and arrector pili muscles. Sometimes a moderate and superficial stromal foreign-body reaction to released hair shaft material (Figures 2D-2H).

´Burnout` (n=1; female)

Fibrous tracts in the reticular dermis mirroring the destroyed hair follicle.

In addition, we have immunohistologically investigated 38 biopsies with Mib1 (Ki-67). In contrast to normal skin and early stages of disease (n=5) we found an epithelial reduction of Ki-67 next to the inflammatory process especially in fully developed (n=6 of 22) and late stages of disease (n=9 of 11) (Figures 3A-3D). This is in part likely due to the destruction of hair follicles, especially the bulge region [12], where the follicular stem cells reside, but is similarly also observed in lichen planus without hair follicle involvement (own unpublished observations). In H&E sections of LP, LPP or FFA this is reflected by a reduction of epithelial mitoses (no more than 1 in a 4 mm punch biopsy) especially in late stages of disease. This phenomenon can only be appreciated in a vertical section and is in contrast to other lichenoid dermatoses, eczema and psoriasis (own unpublished data).

In conclusion, histopathology of scarring alopecia is a challenging

field in dermatopathology and regularly requires clinicopathological correlation. In our opinion, a vertical section is mandatory in the investigation of scarring alopecia, especially to establish the correct diagnosis of LPP / FFA.

References

1. Mehregan DA, Van Hale HM, Muller SA (1992) Lichen planopilaris: clinical and pathologic study of forty-five patients. J Am Acad Dermatol 27: 935-942.

2. Tan E, Martinka M, Ball N, Shapiro J (2004) Primary cicatricial alopecias: clinicopathology of 112 cases. J Am Acad Dermatol 50: 25-32.

3. Cevasco NC, Bergfeld WF, Remzi BK, de Knott HR (2007) A case-series of 29 patients with lichen planopilaris: the Cleveland Clinic Foundation experience on evaluation, diagnosis, and treatment. J Am Acad Dermatol 57: 47-53.

4. Tandon YK, Somani N, Cevasco NC, Bergfeld WF (2008) A histologic review of 27 patients with lichen planopilaris. J Am Acad Dermatol 59: 91-98.

5. Kossard S, Lee MS, Wilkinson B (1997) Postmenopausal frontal fibrosing alopecia: a frontal variant of lichen planopilaris. J Am Acad Dermatol 36: 59-66.

6. Samrao A, Chew AL, Price V (2010) Frontal fibrosing alopecia: a clinical review of 36 patients. Br J Dermatol 163: 1296-1300.

7. Poblet E, Jiménez F, Pascual A, Piqué E (2006) Frontal fibrosing alopecia versus lichen planopilaris: a clinicopathological study. Int J Dermatol 45: 375-380.

8. Kang H, Alzolibani AA, Otberg N, Shapiro J (2008) Lichen planopilaris. Dermatol Ther 21: 249-256.

9. MacDonald A, Clark C, Holmes S (2012) Frontal fibrosing alopecia: a review of 60 cases. J Am Acad Dermatol 67: 955-961.

10. Chew AL, Bashir SJ, Wain EM, Fenton DA, Stefanato CM (2010) Expanding the spectrum of frontal fibrosing alopecia: a unifying concept. J Am Acad Dermatol 63: 653-660.

11. Annessi G, Lombardo G, Gobello T, Puddu P (1999) A clinicopathologic study of scarring alopecia due to lichen planus: comparison with scarring alopecia in discoid lupus erythematosus and pseudopelade. Am J Dermatopathol 21: 324-331.

12. Mobini N, Tam S, Kamino H (2005) Possible role of the bulge region in the pathogenesis of inflammatory scarring alopecia: lichen planopilaris as the prototype. J Cutan Pathol 32: 675-679.

13. Harries MJ, Paus R (2010) The pathogenesis of primary cicatricial alopecias. Am J Pathol 177: 2152-2162.

14. Ohyama M (2012) Primary cicatricial alopecia: recent advances in understanding and management. J Dermatol 39: 18-26.

15. Sellheyer K, Bergfeld WF (2006) Histopathologic evaluation of alopecias. Am J Dermatopathol 28: 236-259.

16. Sperling LC, Cowper SE (2006) The histopathology of primary cicatricial alopecia. Semin Cutan Med Surg 25: 41-50.

17. Stefanato CM (2010) Histopathology of alopecia: a clinicopathological approach to diagnosis. Histopathology 56: 24-38.

18. Elston DM, Ferringer T, Dalton S, Fillman E, Tyler W (2005) A comparison of vertical versus transverse sections in the evaluation of alopecia biopsy specimens. J Am Acad Dermatol 53: 267-272.

19. Nguyen JV, Hudacek K, Whitten JA, Rubin AI, Seykora JT (2011) The HoVert technique: a novel method for the sectioning of alopecia biopsies. J Cutan Pathol 38: 401-406.

20. Özcan D, Özen Ö, Seçkin D (2011) Vertical vs. transverse sections of scalp biopsy specimens: a pilot study on the comparison of the diagnostic value of two techniques in alopecia. Clin Exp Dermatol 36: 855-863.

21. Elston DM, McCollough ML, Warschaw KE, Bergfeld WF (2000) Elastic tissue in scars and alopecia. J Cutan Pathol 27: 147-152.

22. Mehregan AH (1978) Histopathology of alopecias. Cutis 21: 249-253.

23. Al-Refu K (2012) Stem cells and alopecia: a review of pathogenesis. Br J Dermatol 167: 479-484.

24. Sellheyer K, Atanaskova-Mesinkovska N, Nelson P, Bergfeld WF (2011) Differential expression of stem cell markers in lichen planopilaris and alopecia areata. Br J Dermatol 165: 1149-1151.